DRUG INFORMATION ASSOCIATION

42nd Annual Meeting

Guidance Compliant eCTDs

Module 2: Summaries

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Outline

- Overview of Module 2
- Guidance/reference documents
- What goes into this Module
- Do’s and Don’ts
- Mapping from the CFR

Essential References

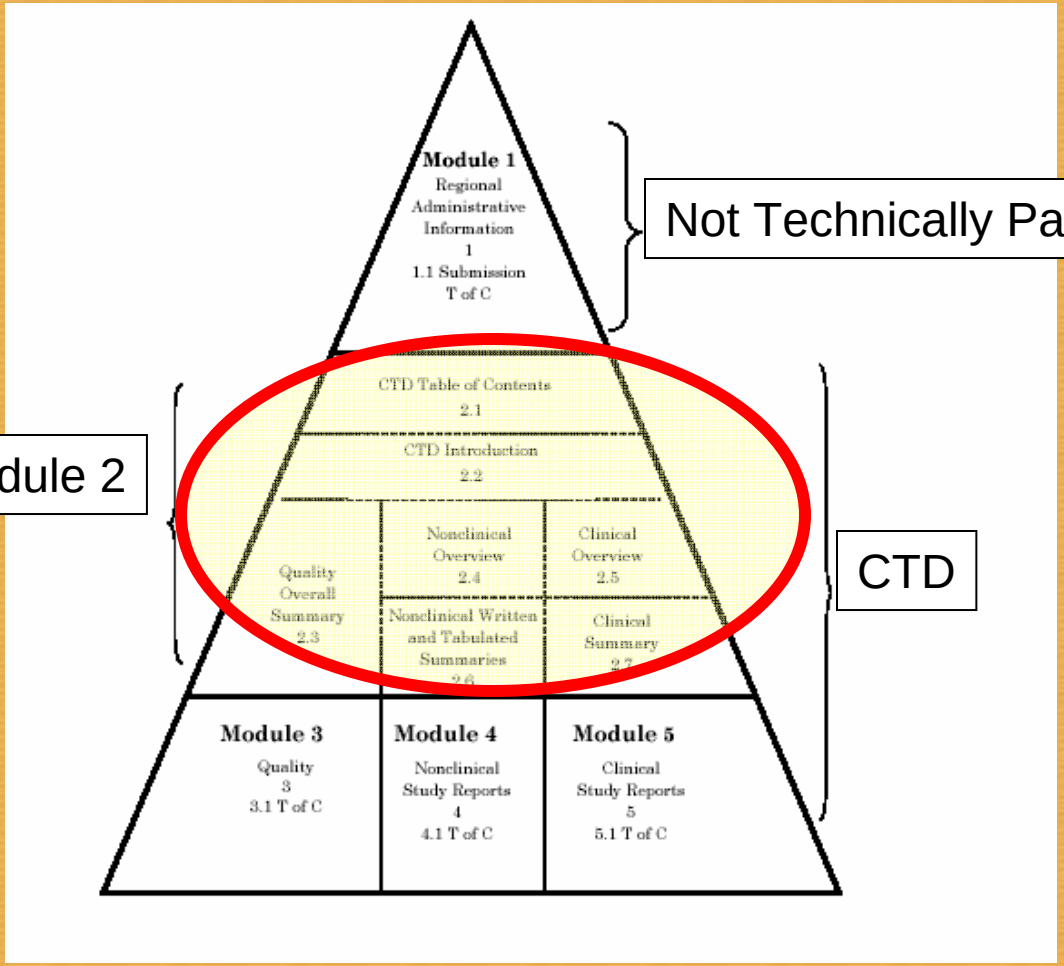
- FDA Guidance for Industry M4: Organization of the CTD
- ICH Harmonised Tripartite Guideline M4 Organisation - includes Granularity Annex
- FDA eCTD Comprehensive Table of Contents Headings and Hierarchy
- ICH M2 EWG, Electronic Common Technical Document Specification

Granularity Annex

Module 2

Module 2	2.1	The TOC is only called for in the paper version of the CTD; there is no entry needed for the eCTD	
	2.2		
	2.3 Note 1	Introduction	
		2.3.S Note 2	2.3.S.1
			2.3.S.2
			2.3.S.3
			2.3.S.4
			2.3.S.5
			2.3.S.6
			2.3.S.7
		2.3.P Note 3	2.3.P.1
			2.3.P.2
			2.3.P.3
			2.3.P.4
			2.3.P.5
			2.3.P.6
			2.3.P.7
			2.3.P.8
		2.3.A	2.3.A.1
			2.3.A.2
			2.3.A.3
		2.3.R	
	2.4		
	2.5		
	2.6	2.6.1	
		2.6.2	
		2.6.3	
		2.6.4	
		2.6.5	
		2.6.6	
		2.6.7	
	2.7	2.7.1	
		2.7.2	
		2.7.3 Note 4	
		2.7.4	
		2.7.5	
		2.7.6	

Module 2 – Starts After Regional



- Module 2 should contain 7 sections in the following order:
  - CTD Table of Contents (2.1)
  - CTD Introduction (2.2)
  - Quality Overall Summary (2.3)
  - Nonclinical Overview (2.4)
  - Clinical Overview (2.5)
  - Nonclinical Written and Tabulated Summaries (2.6)
  - Clinical Summary (2.7)
- The organization of these summaries is described in Guidelines for M4Q, M4S and M4E, available at www.ich.org

Module 3
Quality
Section 2.3
ICH Guidance: M4Q
Concept: Quality

Module 4
Nonclinical
2.4, 2.6
ICH Guidance: M4S
Concept: Safety

Module 5
Clinical
2.5, 2.7
ICH Guidance: M4E
Concept: Efficacy

Module 2
Summarizes

A Summary: Definition

Etymology: Middle English, from Medieval Latin *summarius*, from Latin *summa* sum

1 : **COMPREHENSIVE**; *especially* : covering the main points succinctly

2 a : done without delay or formality : quickly executed <a *summary* dismissal> **b** : of, relating to, or using a summary proceeding <a *summary* trial>

synonym see CONCISE

Source: Merriam-Webster Dictionary

2.1 - 2.2 Introduction and Table of Contents

- TOC (2.1) doesn't exist in eCTD – is already in the XML backbone
- Introduction (2.2) should introduce the pharmaceutical,
  - pharmacologic class
  - mode of action
  - proposed clinical use
- Intro should be 1 page, generally

2.3 Quality Overall Summary

- Include sufficient information from each section to provide the Quality reviewer with an overview of Module 3
- Emphasize critical key parameters of the product
- Provide justification where guidelines were not followed
- Key issues integrating supporting information from other Modules
- Cross-reference to volume and page number in other Modules

2.3 Quality Overall Summary

- “should not exceed 40 pages of text, excluding tables and figures”
- “should not exceed 80 pages” for biotech and products manufactured using more complex processes

2.4 Nonclinical Overview

- Should provide an integrated overall analysis of the information in the Common Technical Document
- In general, should not exceed about 30 pages

2.5 Clinical Overview

- relatively short (about 30 pages) but length will depend on complexity of the application
- Use of graphs and concise tables in the body of the text is encouraged for brevity and to facilitate understanding
- It is not intended that material presented fully elsewhere be repeated in the Clinical Overview; cross-referencing to more detailed presentations provided in the Clinical Summary or in Module 5 is encouraged

2.6 Nonclinical Written and Tabulated Summaries

2.6.1 Introduction

- **The aim of this section should be to introduce the reviewer to the pharmaceutical and to its proposed clinical use. The following key elements should be covered:**
  - **Brief information concerning the pharmaceutical's structure (preferably, a structure diagram should be provided) and pharmacologic properties**
  - **Information concerning the pharmaceutical's proposed clinical indication, dose, and duration of use**

2.6 Nonclinical Written and Tabulated Summaries

2.6.2 Pharmacology written summary
2.6.3 Pharmacology tabulated summary
2.6.4 Pharmacokinetic written summary
2.6.5 Pharmacokinetic tabulated summary
2.6.6 Toxicology written summary
2.6.7 Toxicology tabulated summary

- 100-150 pages for the 3 written summaries

2.7 Clinical Summary Guidance: M4E

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

2.7.2 Summary of Clinical Pharmacology Studies

2.7.3 Summary of Clinical Efficacy [indication]

2.7.4 Summary of Clinical Safety

2.7.5 References

2.7.6 Synopses of individual studies

- **Excluding attached tables, the Clinical Summary will usually be in the range of 50 to 400 pages**

Granularity: A Practical Issue

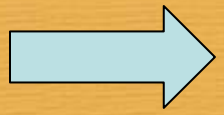
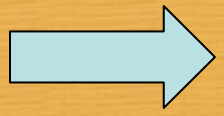
(see ICH M2 EWG, Electronic Common Technical Document Specification)

- 2.7 Clinical Summary
  - 2.7.3 Summary of Clinical Efficacy
    - 2.7.3.1 Background and Overview of Clinical Efficacy
    - 2.7.3.2 Summary of Results of Individual Studies
    - 2.7.3.3 Comparison and Analyses of Results Across Studies
    - 2.7.3.4 Analysis of Clinical Information Relevant to Dosing Recommendations
    - 2.7.3.5 Persistence of Efficacy and/or Tolerance Effects
    - 2.7.3.6 Appendix

Module 2: Things to Do

- Do summarize Modules 3, 4 & 5
- Make your points in sum and *refer* to (don't repeat) details in other sections
- Use leaf titles for differentiation of documents at the same level
- Ensure your Module 2 meets the definition of a summary

Module 2: Things Not to Do

- Don’t include 10,000 pages of detailed patient profiles and other data
- Patient data  Module 5
- ISS and ISE  Module 5
- Don’t use node extensions
- Don’t combine documents together at too high a granularity level

Mapping from the Code of Federal Regulations (CFR)

- 312. -- IND
- 314. – NDA
- These are works in progress
- Refer to Comprehensive Table of Contents Headings and Hierarchy (www.fda.gov)

Mapping Summaries: 312. -- IND

CFR		eCTD	
312.23(a)(3)(i)	Introductory statement	2.2	Introduction to summary
312.23(a)(3)(ii-iv)	Introductory statement	2.5	Clinical overall summary
312.23(a)(8)	Pharmacology and toxicology information	2.4	Nonclinical overview
312.23(a)(8)	Pharmacology and toxicology information	2.6	Nonclinical written and tabulated summaries [use appropriate sections]
312.23(a)(9)	Previous human experience	2.7	Clinical summary [use appropriate sections]

Mapping Summaries: 312. -- NDA

CFR		eCTD	
314.50(c)(2)(ii) to (ix)	Summaries…	A.N.	Use the appropriate sections
314.50(d)(7)	Pediatric use section	2 & 5	Use appropriate sections
314.60	Amendments to an unapproved application	A. N.	Use appropriate sections
314.70 and 314.71	Supplements and other changes to approved applications	A.N.	Use appropriate sections
314.96	Amendments to an unapproved application	A.N	Use appropriate sections

A.N. – As Needed

In Summary

- Use succinct summaries to make your point
- Save patient and study detail for Module 5
- The ISS and ISE go in Module 5
- Read and understand the specifications
- Avoid node extensions
- Structure your eCTD to the lowest level of granularity the specs describe
- Contact FDA for help with questions, esub@cder.fda.gov